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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/215 | A1

(11) International Publication Number: WO 00/04898

(43) International Publication Date: 3 February 2000 (03.02.00)

(21) International Application Number: PCT/US99/16143

(22) International Filing Date: 16 July 1999 (16.07.99)

(30) Priority Data:
60/093,594 21 July 1998 (21.07.98) US

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(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

(57) Abstract

Combinations of a prostaglandin, prostaglandin derivative, a hypotensive lipid derived from a prostaglandin or prostaglandin derivative or an ophthalmologically acceptable salt thereof, a β-adrenergic antagonist or an ophthalmologically acceptable salt thereof and a topical carbonic anhydrase inhibitor or an ophthalmologically acceptable salt thereof are particularly useful in the treatment of ocular hypertension and glaucoma. The combinations are characterized by an improved effect and reduced side-effects.

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TITLE OF THE INVENTION

OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

BACKGROUND OF THE INVENTION

Glaucoma is a degenerative disease of the eye wherein the intraocular pressure is too high to permit normal eye function. As a result, damage may occur to the optic nerve head and result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by the majority of ophthalmologists to represent merely the earliest phase in the onset of glaucoma.

Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. The early methods of treatment of glaucoma employing pilocarpine produced undesirable local effects that made this drug, though valuable, unsatisfactory as a first line drug. β-adrenergic antagonists are also effective in reducing intraocular pressure. While many of these agents are effective for this purpose, there exist some patients with whom this treatment is not effective or not sufficiently effective. Many of these agents also have other characteristics, e.g., membrane stabilizing activity, that become more apparent with increased doses and render them unacceptable for chronic ocular use.

The ß-adrenergic antagonist (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol, timolol, was found to reduce intraocular pressure and to be devoid of many unwanted side effects associated with pilocarpine and, in addition, to possess advantages over many other ß-adrenergic antagonists, e.g., to be devoid of local anesthetic properties, to have a long duration of activity, and to display minimal loss of effect with increased duration of dosing.

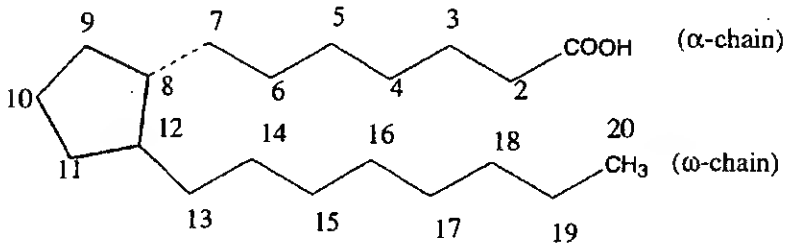
Although ß-adrenergic antagonists reduce intraocular pressure, it does not manifest its action by inhibiting the enzyme carbonic anhydrase, and thus they do not take advantage of reducing the

contribution to aqueous humor formation made by the carbonic anhydrase pathway.

Agents referred to as carbonic anhydrase decrease the formation of aqueous humor by inhibiting the enzyme carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat intraocular pressure by systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such a gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated intraocular pressure, or when no other agent is effective.

Recently, a topically effective carbonic anhydrase inhibitor has become available for clinical use. (*S,S*)-(-)-5,6-Dihydro-4-ethylamino-6-methyl-4*H*-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride (dorzolamide HCl; MK507) is the active ingredient in TRUSOPT™ which is prescribed for the treatment of elevated intraocular pressure in ocular hypertension, open-angle glaucoma and pseudo-exfoliative glaucoma. Topically effective carbonic anhydrase inhibitors, for example disclosed in U.S. Patent Nos. 4,386,098; 4,416,890; 4,426,388; 4,668,697; and 4,863,922 and 4,797,413, are now preferred.

Prostaglandins, or Pgs, are members of a class of organic carboxylic acids that are contained in human and most other mammalian tissues or organs and that exhibit a wide range of physiological activities. Naturally occurring Pgs possess a common structural feature, the prostanoic acid skelton, depicted in Formula I below:



(1)

Some synthetic analogues have somewhat modified skeletons. The primary PG's are classified based on the structural

feature of the five-membered cycle moiety into PGA's, PGB's, PGC's, PGD's PGE's, PGF's PGG's PGH's PGI's and PGJ's and also on the presence or absence of unsaturation and oxidation in the chain moiety as:

Subscript 1 13,14-unsaturated-15-OH,
Subscript 2 5,6- and 13,14-diunsaturated -15-OH,
Subscript 3 5,6-13,14-, and 17,18-triunsaturated-15-OH

Further, PGFs are subclassified as α or β according to the configuration of the hydroxy group at position 9.

Prostaglandins and prostaglandin derivatives are known to lower intraocular pressure. U.S. Patent 4,883,819 to Bito descibes the use and synthesis of PGAs, PGBs and PGCs in reducing intraocular pressure. U.S. Patent 4,824,857 to Goh et al. describes the use and synthesis of PGD2 and derivatives thereof in lowering intraocular pressure including derivatives wherein C-10 is replaced with nitrogen. U.S. Patent 5,001,153 to Ueno et al. describes the use and synthesis of 13,14-dihydro-15-keto prostaglandins and prostaglandin derivatives to lower intraocular pressure. U.S. Patent 4,599,353 describes the use of eicosanoids and eicosanoid derivatives including prostaglandins and prostaglandin inhibitors in lowering intraocular pressure.

Prostaglandin and prostaglandin derivatives lower intraocular pressure by increasing uveoscleral outflow. This is true for both the F type and A type of Pgs and hence presumably also for the B,C,D,E and J types of prostaglandins and derivatives thereof. A problem with using prostaglandin derivatives to lower intraocular pressure is that these compounds often induce an initial increase in intraocular pressure.

Since the carbonic anhydrase inhibitor lowers intraocular pressure without accompanying transient ocular hypertension exhibited by the primary Pgs, and since ß-adrenergic antagonists reduce intraocular pressure by manifesting its action by inhibiting a different enzyme than that of the carbonic anhydrase, the combination of the

carbonic anhydrase inhibitor, ß-adrenergic antagonists and the prostaglandin derivative can be used for the treatment of diseases and conditions in which the lowering of intraocular pressure is desired, for example glaucoma, ocular hypertension and other disease accompanied by an increase in intraocular pressure.

Thus, when a carbonic anhydrase inhibitor, which takes advantage of reducing the contribution to aqueous humor formation made by the carbonic anhydrase pathway, and a ß-adrenergic antagonist, which takes advantage of reducing the contribution to aqueous humor formation made by the ß-adrenergic pathway, is combined with a prostaglandin or prostaglandin derivative, which increases the outflow of aqueous humor, there is experienced an effect that reduces intraocular pressure below that obtained by any of the medicaments individually.

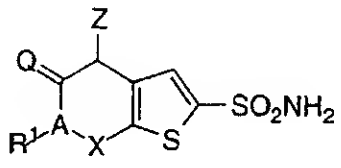
The combinations disclosed herein are effective either by co-administration of the medicaments in one solution or as a combined therapy achieved by prior administration of one of the components, followed by administration of a different component and ending with the administration of the last component until all three components have been administered. The order in which each component is administered can be varied. For example, as a combined therapy, a carbonic anhydrase inhibitor could be the first administered component, followed the administration of a prostaglandin and ending with the administration of a ß-adrenergic antagonist. The use of a single solution containing the three active medicaments is preferred.

There exists a patient population who will benefit from a combination where the minimal dosage of one, two or three of the medicaments is employed, thus minimizing the possibility of the occurrence of undesirable effects of one, two or three of the medicaments which would be more likely to become apparent with chronic use at the higher dosage.

SUMMARY OF THE INVENTION

This invention relates to novel ophthalmic compositions comprising a pharmaceutically acceptable carrier, a topical carbonic anhydrase inhibitor or an ophthamologically acceptable salt thereof, a ß-adrenergic antagonist or an ophthamologically acceptable salt thereof and a prostaglandin or prostaglandin derivative thereof such as a hypotensive lipid derived from PGF2α prostaglandins.

In one aspect of the invention a composition comprising 0.025 to 5% (w/w) of a compound of the structural formula II



(II)

an individual diastereomer, an individual enantiomer or mixture thereof, or an ophthalmologically acceptable salt thereof, wherein:
A is carbon or nitrogen, preferably carbon;
Z is -NHR or -OR, preferably -NHR;
R is C_{1-6}alkyl, either straight or branched chain, preferably C_{2-4}alkyl such as ethyl, propyl or isobutyl;
Q is (H, H), oxo or thioxo;
R^1 is

(a) hydrogen,

(b) C_{1-3}alkyl, preferably methyl, ethyl or n-propyl, or

(c) C_{1-4}alkoxy-C_{1-4}alkyl, preferably 3-methoxypropyl or ethoxymethyl; and X is $-S(O)_2-$ or -C(O)-, preferably $-S(O)_2-$; 0.01 to 1.0% of a ß-adrenergic antagonist such as betaxolol, bufenolol, carteolol, levobunolol, metipranolol, timolol or an ophthalmologically acceptable salt thereof, preferably betaxolol or timolol, 0.005 to 2% (w/w) of a prostaglandin such as 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF2α ester, or 13, 14-dihydro-15-keto-20-ethyl-PGF2α, or a prostaglandin derivative such as a hypotensive lipid derived from PGF2α prostaglandins and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic

material is disclosed. Said composition can optionally contain a gum belonging to the group consisting of gellan gum or xanthan gum.

Another aspect of the invention is concerned with the use of the novel ophthalmic compositions in the treatment of ocular hypertension or glaucoma.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to novel ophthalmic combinations comprising a pharmaceutically acceptable carrier, a topical carbonic anhydrase inhibitor or an ophthamologically acceptable salt thereof, ß-adrenergic antagonist or an ophthamologically acceptable salt thereof and a prostaglandin or prostaglandin derivative thereof, which are used in the treatment of ocular hypertension and glaucoma.

Another aspect of this invention is realized when in the compounds of structural formula II A is carbon; and wherein R is -CH_2CH_3 and R' is -CH_3; or R is -$CH_2CH_2CH_3$ and R' is -$CH_2CH_2CH_2OCH_3$; or R is -CH_2CH_3 and R' is -$CH_2CH_2CH_3$; or R is -$CH_2CH_2(CH_3)_2$ and R' is hydrogen; or R is -CH_2CH_3 and R' is -$CH_2OCH_2CH_3$; and carbons 4 and 6 of the topical carbonic anhydrase inhibitor both have *S* absolute stereochemical configuration.

Another aspect of this invention is realized when in the compounds of structural formula II A is nitrogen; and wherein R is -CH_2CH_3 and R' is -CH_3; or R is -$CH_2CH_2CH_3$ and R' is -$CH_2CH_2CH_2OCH_3$; or R is -CH_2CH_3 and R' is -$CH_2CH_2CH_3$; or R is -$CH_2CH_2(CH_3)_2$ and R' is hydrogen; or R is -CH_2CH_3 and R' is -$CH_2OCH_2CH_3$.

A preferred topical carbonic anhydrase inhibitor for use in the novel compositions of the present invention is 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material.

The carbon atoms to which Z and R^1 are bonded may be chiral. When named according to absolute configuration, e.g., (*R,S*) or (*S,S*), the first letter represents the chirality the carbon atom to which Z is bonded and the second letter represents the chirality of A when A is carbon. The carbonic anhydrase inhibitors of this invention accordingly may be used as diastereomeric mixtures or single enantiomers or as racemic mixtures.

Still another aspect of this invention is realized when the prostaglandin is11, 15-dipivaloyl PGF2α,
11-pivaloyl prostaglandin F2α hydroxyethyl ester,
(+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate,
[1α,2β,3α,5α]methyl-5-cis-2-(phenylethylsulfonamidomethyl)-3,5-dihydroxycyclopentyl heptenoate,
(+-)-5-[6-(1-hydroxy)hexyl)-1,3-benzodioxol-5-yl]-pentanol,
15-pivaloyl PGFα,
7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid,
isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate,
13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF2α esters,
13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester,
(+)-isopropyl fluprostenol,
[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate,
13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters,
or
13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate.

Another aspect of this invention is realized when hypotensive lipids derived from a prostaglandin or prostaglandin derivative such as lipids derived from $PGF_{2\alpha}$ prostaglandins, in which the carboxylic acid group on the α-chain link of the basic prostaglandin

structure is replaced with electrochemically neutral substituents, is used. An example of a hypotensive lipid is that in which the carboxylic acid group is replaced with a C_{1-6} alkoxy group such as OCH_3 (PGF_{2a} 1-OCH_3), or a hydroxy group (PGF_{2a} 1-OH).

In another aspect of this invention, the novel ophthalmic compositions of this invention comprise a pharmaceuticallly acceptable carrier, a therapeutically effective amount of 7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid; isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate; (+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate; 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate; (+)-isopropyl fluprostenol; 13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters; [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate; or hypotensive lipids derived from a prostaglandin or prostaglandin derivative such as lipids derived from $PGF_{2\alpha}$ prostaglandins wherein the COOH is replaced with electrochemically neutral substituents like C_{1-6} alkoxy or hydroxy, ß-adrenergic antagonists such as betaxolol, bufenolol, carteolol, levobunolol, metipranolol, timolol or an ophthalmologically acceptable salt thereof and a topical carbonic anhydrase inhibitor belonging to the group consisting of 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material.

The term "prostaglandin or prostaglandin derivative", within this invention refers to those naturally occurring prostaglandins that are useful for lowering intraocular pressure, specifically prostaglandins A,B,C,D,E,F and J class as well as synthetically modified prostaglandins including but not limited to 15-keto (oxo group in place

of OH at 15) 13,14-dihydro (single bond in place of double bond between positions 13 and 14), and esters thereof.

Prostaglandins of the F class, particularly $PGF_{2\alpha}$ derivatives are known to be particularly potent at lowering intraocular pressure. $PGF_{2\alpha}$ prostaglandin derived hypotensive lipids, in which the carboxylic acid group on the α-chain link of the basic prostaglandin structure is replaced with electrochemically neutral substituents, are also known to be particularly potent at lowering intraocular pressure. In particular, the hypotensive lipids intended for the claimed invention are those compounds which increase aqueous humor outflow without any meaningful interaction with the FP prostaglandin receptor and little or no stimulation of the other prostanoid receptors (DP, EP1-4, IP, TP). Examples of such lipids are taught in US Patent Nos. 4,494,274; 5,034,413; 5,656,635; 5,516,791, 5,385,945, 5,688,819, 5,352,708 and 5,607978 all incorporated herein by reference.

Although Formula I shows a basic skeleton having twenty carbon atoms, the prostaglandin compounds used in the present invention are not limited to those having the same number of carbon atoms. The carbon atoms in Formula (1) are numbered 2 to 7 on the (α-chain starting from the α-carbon atom adjacent to the carboxylic carbon atom which is numbered 1 and towards the five membered ring 8 to 12 on the ring starting from the carbon atom on which the α-chain is attached, and 13 to 20 on the ω-chain starting from the carbon atom adjacent to the ring. When the number of carbon atoms is decreased on the α-chain, the number is deleted in order starting from position 2 and when the number of carbon atoms is increased in the α-chain compounds are named as stbstituted derivatives having, substituents at position 1 in place of carboxy group at C-1. Similarly, when the number of carbon atoms is decreased in the ω-chain, the number is deleted in order starting from position 20 and when the number of carbon atoms is increased on the ω-chain, compounds are named as substituted derivatives having respective substituent at position 20. Thus, 13,14-dihydro-15-keto-PG compounds having 10 carbon atoms in the ω-chain are 13,14-dihydro-15-keto-20-ethyl PGs. The term

prostaglandin derivative also includes esters of the C-1 carboxyl group, such as the C_{1-5} alkyl esters.

The hypotensive lipids contemplated by the claimed invention include $PGF_{2\alpha}$ lipid analogs which, unlike $PGF_{2\alpha}$,, exhibit no meaningful interaction with recombinant or constitutively expressed FP receptors (human, moust, cat). Further the $PGF_{2\alpha}$ lipid analogs exhibit only either minimal or absent interaction with other prostanoid receptors (DP, EP_{1-4}, TP). Even with their inability to interact with with prostanoid receptors the subject $PGF_{2\alpha}$ lipid analogs, having electrochemically neutral substituents, are potent and efficacious at lowering elevated intraocular pressure (IOP). Examples of such lipids are taught in US Patent Nos. 4,494,274; 5,034,413; 5,656,635; 5,385,945, 5,688,819, 5,352,708 and 5,607978 all incorporated herein by reference. A particular ocular hypotensive agent is referred to as AGN 192024, disclosed in VanDenburgh et al., Investigative Oph. and Vis. Sci. March 15, 1998, Vol. 39, No.4. p. S258 abstract 1177 and at the May 10-15, 1998 Association for Research in Vision and Ophthalmology (ARVO) meeting by Allergan of Irvine, California.

The novel ophthalmic formulations of this invention comprise about 0.025 to 5% (w/w), usually about 0.5 to 3% (w/w) and more preferably about 0.7 to about 2% (w/w) of the carbonic anhydrase inhibitors discussed herein, preferably 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material, 0.01 to 1.0%, preferably about 0.1 to 0.5% (w/w) of a ß-adrenergic antagonist such as betaxolol, bufenolol, carteolol, levobunolol, metipranolol, timolol or an ophthalmologically acceptable salt thereof, and about 0.001 to 2.0% (w/w), preferably about 0.1 to 1% (w/w) of the prostaglandin or prostaglandin derivatives discussed herein, preferably 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF2a esters or 13, 14-dihydro-15-keto-20-ethyl-PGF2α

isopropryl esters, and more preferably isopropyl 7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid; isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate; (+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate; 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate, (+)-isopropyl fluprostenol; 13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters; [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate; or a hypotensive lipid derived from a prostaglandin or prostaglandin derivative such as lipids derived from $PGF_{2\alpha}$, prostaglandins, in which the carboxylic acid on the α-chain has been replaced by an electrochemically neutral substituent, to be administered on a 1 to 2 times a day schedule.

A novel method of this invention comprises the topical ocular administration of about 0.025 to about 5 mg per day, preferably about 0.25 to about 3 mg per day of a carbonic anhydrase inhibitor, concomitant, prior or previous administration of about 0.005 to about 1 mg per day, preferably about 0.05 to about 0.5 mg per day of β-adrenergic antagonist and concomitant, prior, or previous administration of about 0.001 to 2 mg per day, preferably about 0.1 to 1.0 mg per day, of prostaglandin or prostaglandin derivative to each eye.

Suitable subjects for the administration of the formulation of the present invention include mammals, primates, man, and other animals, particularly man and domesticated animals such as cats and dogs. For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of each active component or some submultiple thereof.

Typical ophthalmologically acceptable carriers for the novel formulations are, for example, water, mixtures of water and

water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzyldodecinium bromide, benzyl alcohol, phenylethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetate, or gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetra acetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehhicles and the like.

The formulation may also include a gum such as gellan gum at a concentration of 0.1% to 2% by weight so that the aqueous eyedrops gel on contact with the eye, thus providing the advantages of a solid ophthalmic insert as described in U.S. Patent 4,861,760.

The formulation may also include a gum such as xanthan gum at a concentration of 0.1 to 2%, preferably 0.4 to 0.7%(w/w). Particularly preferred is KELTROL™T xanthan gum from Monsanto Performance Materials. The formulation of the instant invention employing xanthan gum will be a hypotonic solution, with a freezing point depression between about -0.28°C and -0.4°C, and preferably between about -0.31°C and -0.37°C. Alternatively, the hypotonicity of the ophthalmic solutoins of the present invention employing xanthan gum will be between about 150 and 215 mOs/kg, and preferably

between 170 and 200 mOs/kg. Coventional ophthalmic solutions are usually prepared as isotonic solutions using tonicity adjusting agents as potassium chloride, sodium chloride, mannitol, dextrose and glycerin. An isotonic solution will have a freezing point depression of approximately -0.54 C. Tonicity may also be measured by the osmolality of the solution, an isotonic solution having an osmolality of about 290 milliosmoles per kilogram (mOs/kg).

The pharmaceutical preparation may also be in the form of a solid insert such as one which after dispensing the drug remains essentially intact as described in U.S. Patents 4,256,108; 4,160,452; and 4,265,874; or a bio-erodible insert that either is soluble in lacrimal fluids, or otherwise disintegrates as described in U.S. Patent 4,287,175 or EPO publication 0,077,261.

The pharmaceutical preparation may also be in the form of a suspension utilizing carbonic anhydrase inhibitors (CAI's) having aqueous solubilities greater than 10 μg/mL but less than 1000 μg/mL at pH 7.4, octanol/water distribution coefficients (DC) measured at pH 7.4 of from 1.0 to 150 and dissociation constants (K_i) of 1.0 nM or lower. The aqueous solubility is measured, for example, by mixing the CAI, in its neutral or salt form in 0.1M phosphate buffer at a pH of 7.4. The mixture is then agitated for approximately 16 to 24 hours, while maintaining a pH of 7.4. If the mixture is a solution, a small amount of a seed crystal of the neutral CAI is added and the mixture is stirred for approximately 16 to 24 hours. The solid/liquid mixture is filtered throught a 0.45 μm filter and the filtrated is assayed by HPLC against standards. The solubility as measured includes both the neutral and ionized forms of the CAI. Under these conditions, at pH 7.4, the CAI's employed for the suspension are predominantly unionized, with the possibility of 10 to 20% of the anionic sulfonamide present (depending on the pKa of the primary sulfonamide group). By way of an example, the suspension encompassed within the meaning of this invention is one which comprises 0.1-10.9 wt% of a carbonic anhydrase inhibitor and 0.01-10.0 wt.% of a polyethoxylated derivative of castor oil resulting

from the reaction of from 2-200 moles of ethylene oxide per 1 mole of castor oil, wherein the derivatives can be hydrogenated.

The measure of the dissociation constant is determined using the fluorescence competition assay which uses the fluorescent HCAII:dansylamide complex and is well known in the art, Chen et al., J. Biol. Chem., 242, 5813 (1967) and Ponticello et al., J. Med. Chem., 30, 591 (1987). The relative K_is for the suspension are less than 3.3.

The following examples of ophthalmic formulations are given by way of illustration and are not limitative of the invention.

EXAMPLE 1

SOLUTION COMPOSITION	I	II	III
(S,S)-(-)-5,6-dihydro-4-ethyl-amino-6-methyl-4H-thieno-[2,3b]thiopyran-2-sulfonamide-7,7-dioxide monohydrochloride (carbonic anhydrase inhibitor)	22.26 g	22.26 g	1.113 g
13,14-dihydro-15-keto-20-ethyl-PGF2. isopropyl ester (prostaglandin derivative)	10.0 g	1.0 g	1.0 g
(s)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	6.834 h	1.367 g	6.834 g
Sodium citrate.2H2O	2.940 g	2.940 g	2.940 g
Benzalkonium Chloride	0.075 g	0.075 g	0.075
Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g

Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
Mannitol	16.00 g	21.00 g	35.90 g
Water for injection q.s. ad.	1000 g	1000 g	1000 g

The active compounds, phosphate buffer salts, benzalkonium chloride, and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted 30 to volume. The composition is rendered sterile by filtration through a sterilizing filter.

EXAMPLES 2-7

Following the procedures of Example 1, solutions are prepared substituting the compounds below for the carbonic anhydrase inhibitors:

Compound	Example *No.*
(S,S)-(-)-5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	2
(S,S)-(-)- 3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	3
R-(+)-3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	4

R-(+)-3,4-dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	5
(S,S)-(-)-5,6-dihydro-4-ethylamino-6-propyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	6
2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide	7

EXAMPLE 8(Suspension)

	CONCENTRATION (WT/V%)
R-(+)-4-ethylamino-3,4-dihydro-2-(3-methoxy) propyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide	2%+2% xs
(s)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (β-adrenergic antagonist)	0.5%
13,14-dihydro-15-keto-20-ethyl-PGF2α isopropyl ester (prostaglandin derivative)	0.5%
Hydroxypropylmethylcellulose	3%
Dibasic Sodium Phosphate	0.2%

Sodium Chloride	0.7%
Disodium Edetate	0.01%
Polysorbate 80	0.05%
Benzalkonium Chloride	0.01%
NaOH/HCl	pH adjust
Purified Water	q.s. 100%

The suspension may be prepared by heating 400 mL of purified water to boiling. HPMC (30.0g) is added and the mixture stirred vigorously until homegeneous. To this is added a solution consisting of sodium chloride (7.0 g), dibasic sodium phosphate (2.0g), disodium edta (0.1g), polysorbate 80 (0.5g) and benzalkonium chloride (10.5 mL of a 1% solution) and purified water is added to a final volume of 900 mL. The mixture is stirred and cooled in an ice bath to room temperature and the pH is adjusted to 7.2 employing HCl (3.5 mL of a 1 N solution. The mixture is q.s. to the final weight with purified water (total 1010g) and filtered through a 10 micron filter. The formulation is prepared by the addition of the above HPMC vehicle (15.014 g) to the above TCAI (0.3074 g) and prostaglandin (1.0 g) and the mixture ias ball milled with 3 mm glass beads (5 g) for approximately 45 hours.

EXAMPLES 9-13

Following the procedures of Example 1, solutions are prepared substituting the compounds below for the prostaglandin derivative

Compound	Example No.
PGF2α,-l-isopropyl ester	9
PGA2	10
13,14-dihydro-15-keto-PGE2 methyl ester	11
15-keto-PGF2α	12
PGF2α tromethamine salt	13
PGA1	14
PGF2α derived hypotensive lipid	15
(+)-isopropyl fluprostenol	16
[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate;	17

EXAMPLE 18

SOLUTION COMPOSITION	I	II
5,6-dihydro-4-ethylamino 6-methyl-4H-thieno[2,3b]thiopyran-		

2-sulfonamide-7,7-dioxide monohydrochloride (carbonic anhydrase inhibitor)	2.0 mg	0.2 mg
(s)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (β-adrenergic antagonist)	0.6 mg	0.1 mg
13,14-dihydro-15-keto-20-ethyl-PGF2α isopropyl ester trimethylphenol-l-acetate	0.1 mg	1.0 mg
Gelrite™ gellan gum	6.0 mg	6.0 mg
Monobasic sodium phosphate	Quantity sufficient to give .2H20	
Dibasic sodium phosphate .12H20	final pH	5.5 - 6.0
Benzyldodecinium bromide	0.10 mg	0.10 mg
Polysorbate 80	0.2 mg	0.2 mg
Water for injection q.s. ad.	1.0 mL	1.0 mL

The active compounds, Gelrite' gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

EXAMPLES 19-24

Following the procedures of Example 16, solutions are prepared substituting the compounds below for the carbonic anhydrase inhibitors:

Compound	Example No.
(S,S)-(-)-5,6-dihydro-4-ethylamino-6-methyl-4H-thien6[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	19
3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1 dioxide hydrochloride	20
R-(+)-3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	21
R-(+)-3,4-dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	22
(S,S)-trans-5,6-dihidro-4-ethylamino-6-propyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7- dioxide	23
2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide	24

EXAMPLES 25-33

Following the procedures of Example 16, solutions are prepared substituting the compounds below for the prostaglandin derivative.

Compound	Example
PGF2α,-l-isopropyl ester	25
PGA2	26
13,14-dihydro-15-keto-PGE2 methyl ester	27
15-keto-PGF2α	28
PGF2α tromethamine salt	29
PGA_1	30
PGF2α derived hypotensive lipid	31
(+)-isopropyl fluprostenol	32
[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate;	33

EXAMPLE 34

SOLUTION COMPOSITION	I	II
5,6-dihydro-4-ethylamino 6-methyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide monohydrochloride (carbonic anhydrase inhibitor)	2%	2%
4-[2-hydroxy-3-(1-methylethyl)-amino]-propoxyl]-2,3,6-trimethylphenol-1-acetate	0.6%	0.6%
13,14-dihydro-15-keto-20-ethyl-PGF2α isopropyl ester trimethylphenol-1-acetate	0.1 %	1.0 %
Xanthan gum	0.5%	0.7%
Sodium Chloride	0.2%	0.2%
Benzalkonium Chloride	0.0075%	0.0075%
Sodium Hydroxide	qs pH5.6	pH 5.6
Water	qs 100%	100%

The active compounds, sodium chloride and benzalkonium chloride are dissolved in water for injection. The pH of the composition is adjusted to 5.6 by addition of 0.2N sodium hydroxide solution, and water for injection is added until the weight of the composition is equal to 75 parts of the final weight (I) or 65 parts of the final weight (II). The composition is sterilized by filtration, and the solution flushed with sterile nitrogen. Then a clarified, steam sterilized concentrate of 2%

xanthan gum is added to the solution of drug and the resulting solution is homogenized by stirring. The solution is aseptically subdivided into sterile vials and sealed.

EXAMPLES 35-40

Following the procedures of Example 30, solutions are prepared substituting the compounds below for the carbonic anhydrase inhibitors:

Compound	Example No.
(S,S)-(-)-5,6-dihydro-4-ethylamino-6-methyl-4H-thien6[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	35
3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1 dioxide hydrochloride	36
R-(+)-3,4-dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-l,l-dioxide hydrochloride	37
R-(+)-3,4-dihydro-4-ethylamino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-l,l-dioxide hydrochloride	38
(S,S)-trans-5,6-dihidro-4-ethylamino-6-propyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7- dioxide	39

2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide	40

EXAMPLES 41-47

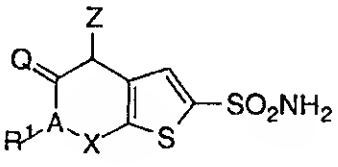
Following the procedures of Example 30, solutions are prepared substituting the compounds below for the prostaglandin derivative.

Compound	Example
PGF2α-I-isopropyl ester	41
PGA2	42
13,14-dihydro-15-keto-PGE2 methyl ester	43
15-keto-$PGF_{2\alpha}$	44
$PGF_{2\alpha}$ tromethamine salt	45
PGA1	46
$PGF_{2\alpha}$ derived hypotensive lipid	47
(+)-isopropyl fluprostenol [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate;	48

WHAT IS CLAIMED IS:

1. An ophthalmic formulation for the treatment of ocular hypertension and glaucoma in a subject in need thereof, comprising a pharmaceutically acceptable carrier, a topical carbonic anhydrase inhibitor or an ophthamologically acceptable salt thereof, a ß-adrenergic antagonist or an ophthamologically acceptable salt thereof, and a prostaglandin or prostaglandin derivative thereof or a hypotensive lipid derived from a prostaglandin or prostaglandin derivative.

2. An ophthalmic formulation for the treatment of ocular hypertension and glaucoma in a subject in need thereof comprising 0.025 to 5% (w/w) of a compound of the structural formula II



(II)

an individual diastereomer, an individual enantiomer or mixture thereof, or an ophthalmologically acceptable salt thereof, wherein:
A is carbon or nitrogen;
Z is -NHR or -OR;
R is C_{1-6}alkyl, either straight or branched chain, preferably C_{2-4}alkyl such as ethyl, propyl or isobutyl;
Q is (H, H), oxo or thioxo;
R^1 is

(a) hydrogen,
(b) C_{1-3}alkyl or
(c) C_{1-4}alkoxy-C_{1-4}alkyl; and X is -$S(O)_2$- or -C(O)-; 0.01 to 1.0% of a ß-adrenergic antagonist such as betaxolol, bufenolol, carteolol, levobunolol, metipranolol, timolol or an ophthalmologically acceptable salt thereof, 0.001 to 2% (w/w) of a prostaglandin such as 13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF2α ester, 13, 14-dihydro-15-keto-20-ethyl-PGF2α or prostaglandin derivative such as a

hypotensive lipid derived from PGF2α prostaglandins and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material.

3. A formulation according to claim 2 wherein A is carbon; and wherein R is $-CH_2CH_3$ and R^1 is $-CH_3$; or R is $-CH_2CH_2CH_3$ and R^1 is $-CH_2CH_2CH_2OCH_3$; or R is $-CH_2CH_3$ and R^1 is $-CH_2CH_2CH_3$; or R is $-CH_2CH_2(CH_3)_2$ and R^1 is hydrogen; or R is $-CH_2CH_3$ and R^1 is $-CH_2OCH_2CH_3$; and carbons 4 and 6 of the topical carbonic anhydrase inhibitor both have *S* absolute stereochemical configuration.

4. A formulation according to claim 2 wherein A is nitrogen; and wherein R is $-CH_2CH_3$ and R^1 is $-CH_3$; or R is $-CH_2CH_2CH_3$ and R^1 is $-CH_2CH_2CH_2OCH_3$; or R is $-CH_2CH_3$ and R^1 is $-CH_2CH_2CH_3$; or R is $-CH_2CH_2(CH_3)_2$ and R^1 is hydrogen; or R is $-CH_2CH_3$ and R^1 is $-CH_2OCH_2CH_3$.

5. A formulation according to claim 2 wherein the carbonic anhydrase inhibitor is 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material.

6. A formulation according to claim 2 wherein the prostaglandin is
11, 15-dipivaloyl PGF2α,
11-pivaloyl prostaglandin F2α hydroxyethyl ester,
(+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate,
[1α,2β,3α,5α]methyl-5-cis-2-(phenylethylsulfonamidomethyl)-3,5-dihydroxycyclopentyl heptenoate,
(+-)-5-[6-(1-hydroxy)hexyl)-1,3-benzodioxol-5-yl]-pentanol,

15-pivaloyl PGFα,
7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid,
isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate,
13,14-dihydro-15(R)-17-phenyl-18,19,20-trinor-PGF2α esters,
13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester,
(+)-isopropyl fluprostenol;
13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters;
[2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate, or
13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate.

7. A formulation according to claim 2 in which the prostaglandin derivative is a hypotensive lipid derived from $PGF_{2\alpha}$ prostaglandins wherein the carboxylic acid group on the α-chain link of the basic prostaglandin structure is replaced with electrochemically neutral substituents.

8. A formulation according to claim 2 which comprises a pharmaceuticallly acceptable carrier, a therapeutically effective amount of a prostaglandin which is 7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid;
isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate;
(+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate;
13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate; (+)-isopropyl fluprostenol; 13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters; [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate; or a hypotensive lipid derived from PGF2α prostaglandins,

a ß-adrenergic antagonist such as betaxolol, bufenolol, carteolol, levobunolol, metipranolol, timolol or an ophthalmologically acceptable salt thereof and a topical carbonic anhydrase inhibitor belonging to the group consisting of 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-h]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride or 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide and their trans and cis enantiomers, or an ophthalmologically acceptable salt thereof, including racemic material.

9. The formulation of Claim 2 wherein the concentration of carbonic anhydrase inhibitor is 0.5% to 3%, the concentration of ß-adrenergic antagonist is 0.1 to 0.5% and the concentration of the prostaglandin or prostaglandin derivative is 0.03% to 1.0%.

10. The formulation of claim 2 wherein the carbonic anhydrase inhibitor has an aqueous solubility greater than 10 ug/mL but less than 1000 ug/mL at pH 7.4, and a Ki of 1.0 nM or lower.

11. The formulation of claim 10 which is a suspension.

12. The formulation of claim 2 which optionally contains from about 0.1% to about 2% of gellan gum.

13. The formulation of claim 2 which optionally contains from about 0.1% to about 2% (w/w) of xanthan gum.

14. The formulation of claim 13 which contains from about 0.4 to about 0.7%(w/w) of xanthan gum, said xanthan gum being a hypotonic solution, with a freezing point depression between about -0.28°C and -0.4°C.

15. The formulation of claim 13 wherein the gum is KELTROL™T xanthan gum in a hypotonic solution with a freezing point from about -0.31°C to about -0.37°C.

16. A method of treating ocular hypertension and glaucoma which comprises the topical ocular administration to a patient in need of such treatment of a unit dose of the formulation of Claim 1.

17. A method of treating ocular hypertension and glaucoma which comprises the topical ocular administration to a patient in need of such treatment of a unit dose of the formulation of Claim 2.

18. A method of treating ocular hypertension and glaucoma which comprises the topical ocular administration to a patient in need of such treatment of a unit dose of the formulation of Claim 11.

19. A method of treating ocular hypertension and glaucoma which comprises the topical ocular administration to a patient in need of such treatment of a unit dose of the formulation of Claim 12.

20. A method of treating ocular hypertension and glaucoma which comprises the topical ocular administration to a patient in need of such treatment of a unit dose of the formulation of Claim 13.

21. A formulation which comprises a pharmaceutically acceptable carrier, a topical carbonic anhydrase inhibitor 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno-[2,3-b]thiopyran-2-sulfonamide-7,7 dioxide hydrochloride, a prostaglandin which is 7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid; isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate; (+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate; (+)-isopropyl fluprostenol; 13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters; [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-

[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate; or13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate and a ß-adrenergic antagonist (s)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate.

22. A formulation according to claim 21 which optionally contains gellan gum or xanthan gum.

23. A formulation which comprises a pharmaceutically acceptable carrier, a topical carbonic anhydrase inhibitor 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide, a prostaglandin comprising 7–[3α,5α dihydroxy-2-(3a-hydroxy-5--1E-pentenyl)cyclopentyl]-5Z-heptenoic acid;isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate; (+)-(Z)-sodium-7-[1R, 2R, 3R, 5S)-3,5-dihydroxy-2-[(E)-1-octenyl]cyclopentyl]-5-heptenoate sesquihydrate; 13,14-dihydro-15-keto-20-ethyl-$PGF_{2\alpha}$ isopropyl ester trimethylphenol-1-acetate, (+)-isopropyl fluprostenol; 13,14-dihydro-$PGF_{2\beta}$ isoprpopyl esters; [2R(1E, 3R),3S(4Z),4R]-isopropyl-7-(tetrahydro-2-[4-(3-chlorophenoxy)-3-hydroxy-1-butenyl)-4-hydroxy-3-furanyl]-4-heptanoate; and a ß-adrenergic antagonist (s)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate.

24. A formulation according to claim 23 which optionally contains gellan gum or xanthan gum.

25. A formulation which comprises a pharmaceutically acceptable carrier, a topical carbonic anhydrase inhibitor 2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-4-(ethylamino)-3,4-dihydro-2-(3-methoxypropyl)-1,1-dioxide, a hypotensive lipid derived from $PGF_{2\alpha}$ prostaglandins, in which the carboxylic acid group on the α-chain link of the basic prostaglandin structure is replaced with electrochemically

neutral substituents and a ß-adrenergic antagonist (s)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate.

26. A formulation according to claim 25 which optionally contains gellan gum or xanthan gum.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/16143

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/215
US CL : 514/530
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/530

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,599,353 A (BITO et al.) 08 July 1986, see the entire document.	1-26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search 30 AUGUST 1999	Date of mailing of the international search report 07 OCT 1999
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